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REVIEW

# Management of Soft Tissue Sarcomas of the Extremity in Adults

ALVARO A. VALLE, MD, AND WILLIAM G. KRAYBILL, MD, FACS
*From the Soft Tissue Melanoma and Bone Department, Surgical Oncology Division, Roswell Park Cancer Institute, Buffalo, New York*

Concepts of the current management of soft tissue sarcomas (STS) of the extremities in adults are presented. The roles of surgery, radiation, and chemotherapy as well as the combination of these modalities are reviewed. The addition of radiation therapy to less than radical surgery has resulted in higher rates of limb preservation and acceptable local control. A multidisciplinary approach will help achieve optimal functional results with less morbidity. Treatment of systemic disease is poor with current methods. Innovative uses of existing systemic modalities or new modalities will be important to improve results in the management of these difficult tumors. © 1996 Wiley-Liss, Inc.

KEY WORDS: **surgery, radiation, chemotherapy, limb preservation**

## INTRODUCTION

A total of 6,400 new cases of soft tissue sarcomas (STS) are estimated to occur in the United States during 1996 [1], which constitutes less than 1% of all malignancies. Approximately 50% of these tumors will occur in the extremities [2]. Although the etiology is not well understood, several conditions have been associated with an increased incidence. Genetically transmitted diseases such as neurofibromatosis [3], Gardner's syndrome [4], and tuberous sclerosis [5] have an increased incidence. Although rare, STS have been associated with previous radiation therapy [6]. The M.D. Anderson Cancer Center (MDA) [7] reported 16 cases in 40 years after radiation to the chest wall, which represented 5% of all sarcomas of the chest wall treated during the same period. Lymphangiosarcomas may develop in patients with chronic lymphedema, the most common example being Stewart-Treves syndrome [8]. The possibility of a chemical etiology has been investigated, particularly with phenoxy acids and chlorophenols, but no definite association has been established [9]. A familial cancer syndrome associated with p53 germline mutations appears to have an increased incidence of sarcomas [10].

Histologically, STS are usually classified according to the cell of origin. Although tumor grade is accepted as being most descriptive of behavior, histologic classification may have a role in prognosis and management decisions. For example, as many as 16% of epithelioid sarcomas may metastasize to lymph nodes [11], and these patients may be candidates for elective lymph node dissection. However, for most STS, assessment of tumor grade and tumor size provides an accurate estimate of prognosis.

## CLINICAL BEHAVIOR

In general, the behavior of STS varies according to tumor grade. Low grade sarcomas may recur locally if resected with positive margins [12]. Distant metastasis from these sarcomas are rare. Standard therapy is resection with negative margins. Large, low grade STS may benefit from adjuvant radiation. High grade STS characteristically extend along tissue planes and metastasize hematogenously. High grade extremity sarcomas most commonly metastasize to the lungs. Approximately 20% of new patients with high grade STS will have distant

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Address reprint requests to William G. Kraybill, M.D., Soft Tissue-Melanoma & Bone Department, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263.

metastatic disease at the time of diagnosis [13]. The incidence of nodal metastasis is low for most types of STS. Reports from Memorial Sloan-Kettering Cancer Center (MSKCC) (New York City) have identified an overall 2.6% incidence [11]. Exceptions are epithelioid sarcomas, angiosarcomas, embryonal rhabdomyosarcomas, and synovial sarcomas. These tumors will metastasize to lymph nodes in up to 16% of patients [11], and ~80% of recurrences will be seen within 2 years of diagnosis [14]. High grade lesions that are removed by simple excision without adjuvant therapies have a high local recurrence rate [14].

An understanding of prognostic factors is important in treatment planning. The most important prognostic factors are tumor grade, size, and depth. The original contribution from Russell et al. [15] in 1977 showed a significant difference in survival when tumors were stratified by grade. High tumor grade is a predictor of local and distant failure [16]. In high grade tumors, size correlates well with prognosis, as seen in the study by Greer et al. [17], who reported that small (<5 cm) high grade tumors had a similar survival to small low grade tumors. Work by Suit et al. [18] emphasizes the importance of large size as a poor prognostic factor in high grade STS. In this study, the 5-year actuarial rate of distant metastasis was directly proportional to tumor size. More recent data from MSKCC [19] demonstrate that age, positive margin at the time of resection, presentation with recurrent disease, histological subtype, and location can have statistical significance as prognostic factors for disease specific survival and local recurrence. In another study [20] analyzing subsequent survival and recurrence in those patients that survive >5 years without recurrence, it was found that tumor size and positive microscopic margin were significant predictors of subsequent survival.

Three staging systems have been developed [17,21,22] and all have their proponents. However, the American Joint Committee on Cancer (AJCC) staging system is most commonly used and is the system used by the American College of Surgeons Cancer Program and the National Cancer Data Base. The AJCC system [21], which takes into consideration tumor grade, size, nodal involvement, and metastasis, has been shown to correlate well with survival (Fig. 1) [15].

## CLINICAL PRESENTATION AND EVALUATION

Most patients with STS present with an asymptomatic mass. Evaluation should include a complete history and physical examination, with attention directed toward the area of the primary tumor and areas at risk for metastasis. Further evaluation of the patient includes imaging assessment of the primary tumor and potential sites of metastasis. Both magnetic resonance imaging (MRI) and computed tomography may be used to evaluate the extent of primary tumors of the extremities, but MRI has been demonstrated to have superior sensitivity and equivalent specificity [23]. MRI provides enhanced contrast resolution and multiphasic imaging without the need for intravenous contrast agents and ionizing radiation required by CT scans. However, CT scans may provide adequate assessment of extremity soft tissue sarcomas and may be more accurate in defining cortical bone involvement. Angiography is rarely needed.

To evaluate patients for lung metastasis, computed tomography (CT) is the method of choice [24]. For follow-up, in addition to a careful physical examination, routine chest X-rays complemented by CT when needed are usually sufficient. Proper evaluation and treatment of sarcomas require a biopsy. Four types of biopsy can be performed. Fine-needle aspiration (FNA) and core-needle biopsy have been assessed in a prospective trial. Each patient with an unknown soft tissue mass was evaluated by core-needle biopsy and FNA biopsy prior to excision of the mass [25]. Core-needle biopsy correctly identified all 16 malignant sarcomas and 10 of 11 benign masses. FNA biopsy correctly classified 12 of 14 malignant sarcomas, but only 4 of 11 benign masses (one was indeterminate). Although FNA with immunohistochemistry may be effective in selective institutions with special expertise, core-needle biopsy allows far more complete assessment of the tumor. However, FNA may be useful for the diagnosis of recurrence [25].

Excisional biopsy should be used only when the tumor is small and the entire biopsy site and bed may be removed easily should the mass be malignant. Although the selection of patients for excisional biopsy will depend on anatomic setting, as a rule tumors >2.5 cm in diameter should have incisional or needle biopsy prior to definitive treatment. Inappropriate excisional biopsy may contaminate the planes of future resection, increasing the chance of local recurrence. Incisional biopsies ideally should be performed by the treating surgeon. They should be carefully planned so that the biopsy site may be excised at the time of surgical resection. Careful attention should be given to achieving good hemostasis. Because these are unusual tumors, the interpretation of the biopsy should be done by a pathologist with experience in STS.

## ROLE OF SURGERY

Historically, surgery has been the principal treatment for sarcomas. Local excision was the first method employed, but recurrence rates as high as 93% were reported [14]. With wide resection, the recurrence rate decreased to ~60% [14]. Cantin et al. [26] extensively discussed the behavior of STS treated surgically between 1935 and 1959 at Memorial Cancer Center. In their classic article describing 653 patients treated for cure, there was a 29% local recurrence rate [26]. The importance of anatomic setting of the sarcoma was emphasized in their work. When more aggressive radical compartment resections or amputations were performed, the local failure rate

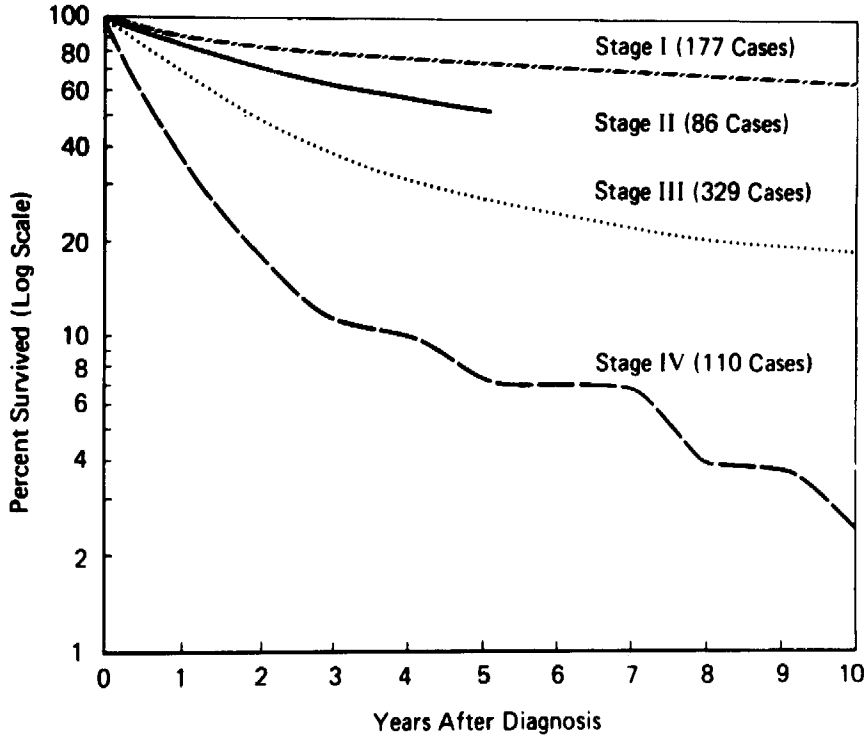


Fig. 1. Survival curves by stage showing good correlation. The curve for Stage II was not plotted beyond 5 years, since at that point the standard error was 5% or higher. Adapted with permission from Russell WO, Cohen J, Enzinger F, et al.: A clinical and pathological staging system for soft tissue sarcomas. Cancer 40:1569, 1977.

decreased to <20% [14,27,28]. Shiu et al. [27] at MSKCC [27] and Simon and Enneking [29], from the University of Florida, reported local control rates above 80%, but with amputation rates as high as 50%. In both of these series, amputation resulted in local recurrence in <10% of patients. In spite of this, distant metastasis developed in at least one-third of these patients. Shiu et al. [27] reported a 41% survival rate at 10 years. Distant metastases were the direct cause of death in 90% of patients who died of their disease. It became evident that even after optimal local control, these patients were at continued risk from distant disease. Because of these issues, alternatives in management were sought to improve quality of life, decrease the amputation rate, and improve survival. Suit et al. [30], Perry and Chu [31], and Lindberg et al. [32] advocated the addition of radiation to conservative surgery. Rosenberg et al. [33] found in a prospective randomized study equivalent results for amputation and conservative surgery with radiation therapy.

Adequate local control remains a priority in the surgical management of STS. Simon et al. [28] defined the different surgical approaches in relation to the margins achieved. An intracapsular excision is an excisional biopsy with grossly positive margins. A marginal resection performed just outside of the capsule of the tumor is likely to have a positive microscopic margin. A wide resection removes the tumor with a variable amount of normal surrounding tissue, usually within the same anatomic compartment. Pathologic margins should be microscopically negative. A radical resection consists of removal of the total anatomic compartment involved by the tumor, which may or may not require amputation. When surgery is used in combination with radiation, frequently a "wide excision" is adequate [34]. The use of these two modalities together decrease morbidity while improving function and maintaining an acceptable local control rate.

Although radiation therapy may reduce the recurrence rates after marginal resections with positive microscopic margins, the best results are seen with microscopically negative surgical margins [34]. In the past, amputation was indicated when neoplasia was intimately related to neurovascular structures [27,35]. Usually with the appropriate utilization of radiation preoperatively or postoperatively, vessels may be dissected free and local control achieved without amputation or resection of major vessels. However, resection of the vessels and replacement with prosthetic graft may be safely performed when necessary [36]. If the nerve is the only structure in question, this may be resected with an acceptable functional deficit. MSKCC presented their experience [37] with the use of

adjuvant brachytherapy (BRT) in 45 patients with this problem. The neurovascular bundle was preserved with limb preservation in 84% and a 9% incidence of radiation neuritis. Lymphadenectomy is generally not indicated unless there is clinical involvement of lymph nodes or the tumor is one with a propensity for lymph node metastasis. The indications for amputation are limited to those patients whose tumor cannot be resected with preservation of a functional extremity [38].

## ROLE OF RADIATION THERAPY

As early as the 1940s and 1950s, radiation therapy (RT) was used sporadically for soft tissue sarcomas [31,39]. Perry and Chu [31] demonstrated that these tumors were definitely responsive to radiation. In 1954, Pack [39] articulated the concept of combining surgery and radiation. Tepper and Suit [40] demonstrated in 1985 that radiation alone with doses >65 Gy can achieve local control in ~43% of patients. However, the ability to obtain local control is inversely proportional to the size of the tumor. For tumors <5 cm, local control may be expected in 88% of patients; in 53% for tumors between 5 and 10 cm; and in 33% for tumors >10 cm. Such high doses of radiation are associated with significant long-term morbidity. In patients that are not surgical candidates, this may be a second line therapy.

As noted, an effort was made to combine less radical surgery with moderate doses of radiation. The goal was to achieve local control with a decreased amputation rate and morbidity. Suit et al. in 1975 [30] and Rosenberg et al. in 1982 [33] demonstrated that limb sparing was feasible when using surgery combined with radiation therapy. In Suit's report [30], the local control rate was 87%. In Rosenberg's prospective randomized trial [33] of amputation versus limb-preserving surgery and radiation, the DFS at 5 years was 71% and 78%, respectively, and the 5-year survival was equivalent: 83% and 88%, respectively. Local recurrence was seen in four cases in the limb preservation group and none in the amputation group. There was no difference in survival.

Since then, different methods of combining radiation and surgery have been used (Table I). External beam radiation therapy may be given preoperatively, intraoperatively, or postoperatively. Brachytherapy (BRT) may be given postoperatively. In the 1980s, several reports showed good results with the addition of RT following conservative surgery. The M.D. Anderson's [41] experience with 200 extremity cases demonstrated a local recurrence rate of 20%, with a functional limb preservation rate of 84.5% and an absolute 5-year disease-free survival (DFS) of 69.4%. Massachusetts General Hospital (MGH) [42] has reported a 5-year local control rate of 90% in 159 patients. At the National Cancer Institute (NCI) [43], the local failure rate was 8% in a series of 123 patients. In a smaller series from the University of California (San Francisco) [44], there was a 10% local failure rate. Several other small series in the recent literature from Europe and the United States reproduced these findings.

Studies from several institutions have shown good results with preoperative radiation. In the MGH series [42], 128 patients treated preoperatively had a 5-year local control rate of 93%. This was especially advantageous in large lesions, where control was 79% for lesions between 15 and 20 cm, and 100% for lesions larger than 20 cm. When recurrent tumors were treated, the local control rate was 82%. The MDA preoperative radiation experience reported by Barkley et al. [45] showed a 90% local control rate. Most of the tumors [89%] treated in this series were >5 cm. In 37% of the cases, the tumors were >15 cm. In the University of Florida [46] series, preoperative radiation was used in 19 patients with extremity sarcomas. Local control was achieved in 94% of patients. The distant failure rate of high grade tumors in the MGH series was ~41% for all patients and was directly related to tumor size. Local control was improved in those patients with negative margins compared to those with positive margins in a report by Sadoski [47]. In 132 patients treated with preoperative RT, the 5-year local control rate for patients with positive margins was 81% compared to 97% in patients with negative margins. In another series from MDA reported by Tanabe et al. [48] in which 95 consecutive patients were treated with preoperative RT followed by conservative surgery, the 5-year local recurrence-free survival was 62% for patients with positive margins compared to 91% in the margin negative patients. Clearly, tumor size and margin are important prognostic indicators in high grade STS of the extremities.

MSKCC pioneered the use of interstitial brachytherapy with afterloading catheters and Iridium 192 [49]. The initial pilot study was followed by a prospective randomized trial comparing brachytherapy after surgical resection versus surgery alone [50]. After complete resection of the tumor with clear margins, the patients were randomized to bracytherapy (BRT) or no radiation. At 5 years the local control was 82% for the treatment group and 69% for the control group ($P = 0.04$). High grade tumors responded better than low grade tumors with a local control rate of 90% in the treatment group vs. 65% for the no BRT group ($P = 0.0025$). BRT had no impact on low grade tumors. There was no difference in distant metastasis ($P = 0.60$) in BRT patients and patients who had not received BRT. It is evident that the significant improvement attained in local control did not translate into improved survival for any category.

In view of these findings, a prospective randomized trial was undertaken to assess the role of brachytherapy in low grade tumors [51]. After surgical resection, 45 patients were randomized to BRT or surgery alone. Local recurrence was 22% for the no BRT and 27% for the BRT group. No difference in local control, proportion

**TABLE I. Soft Tissue Sarcoma of the Extremities in Adults: Combined Treatment Surgery and Radiation for Limb-Sparing Results With Different Radiotherapy Approaches**

| Approach | No. pts. | Limb salvage | Local recurrence | 5-year disease-free survival | Complications |
|---|---|---|---|---|---|
| *Postoperative RT* (Ref) | | | | | |
| MD Anderson [41] | 200 | 84.5% | 20% | 69.4% | 6.5% |
| Massachusetts General Hosp. [42] | 159 | U | 10% | 72% | U |
| National Cancer Institute [43] | 123 | 100% | 8% | 66%[a] | U |
| Univ. CA, San Francisco [44] | 29 | 96% | 10% | 68% | 27% |
| *Preoperative RT* | | | | | |
| MD Anderson [45] | 110 | 95% | 10% | 61%[a] | 14% |
| Massachusetts General Hosp. [42] | 128 | U | 7 | 73% | U |
| Univ. FL [46] | 19 | 94.7% | 5% | 58%[a] | 52% |
| *Brachytherapy* | | | | | |
| Memorial Sloan-Kettering [50] | 78 | U | 17% | 84%[b] | 14% |

[a]Follow-up < 5 yr.
[b]Disease-specific survival.
U = unclear or unstated.

free of recurrence, and overall survival was seen. A retrospective study of 80 low-grade STS of the extremity and torso conducted by the National Cancer Institute (NCI) found no local recurrence in 37 extremity sarcomas after adjuvant postoperative external beam RT. Eight of 28 patients who did not receive RT suffered local recurrence [11]. The beneficial effect was more significant for patients with positive margins. In this study there was no stratification by size. Suit [18] reported no evidence of recurrence in 17 large, low grade tumors treated with postoperative external beam RT [18]. Why BRT is ineffective in controlling low grade tumors is unclear, although it may relate to the percentage of the low grade tumor being in a resistant phase of the cell cycle during the relatively short course of BRT. Patients with low grade tumors who have close or positive margins following resection should be re-resected. If this cannot be achieved with preservation of a functional limb, then external radiation should be considered.

## ROLE OF OTHER THERAPIES IN LOCAL CONTROL

The roles of chemotherapy and biologicals have been assessed for their impact on local control. Following the observation of response rates to Adriamycin in the range of 20–30%, a series of trials were initiated to examine its role in limb salvage at UCLA [52]. In a nonrandomized fashion, 416 consecutive patients were entered into five sequential protocols of neoadjuvant and adjuvant therapy from 1974–1992. The early protocols used intra-arterial infusion of doxorubicin followed by RT in different schedules. The surgical procedure was wide local excision with clear margins. Subsequently, the roles of intra-arterial and intravenous doxorubicin were compared, and no difference was found. Therefore, doxorubicin was given intravenously in the remaining trials and a second drug, cisplatinum, was added. In the most recent trials three drugs were used: two courses of ifosfamide were given followed by RT preoperatively, and then postoperative sequential courses of doxorubicin and cisplatinum were administered. The results as published are excellent. However, because they were not randomized trials, it is difficult to compare the different UCLA protocols with each other and with studies from other centers. The complication rates have depended on radiation dose.

The use of isolated limb perfusion in sarcomas permits high tumor concentration of drugs, with decreased systemic toxicity. There is an extensive experience with the use of this technique in patients with melanoma. Using different drugs, STS have been treated with this modality without obvious advantage over other modalities [53]. Recently it was reported that a three-drug combination using tumor necrosis factor (TNF), interferon gamma, and melphalan was effective for melanoma and sarcoma [54]. The complete response (CR) rate was 89% for both tumors in this small series. The use of this approach in sarcoma patients is not clearly defined, but it may be of significant benefit to a subset of patients with locally advanced disease that are resectable only with amputation. It also may be of value in patients with distant disease who require palliation of the primary tumor. A recent report from the Netherlands [55] using high dose

**TABLE II. Summary of Published Findings in Prospective Randomized Trials of Adjuvant Chemotherapy vs. Observation in Soft Tissue Sarcomas of the Extremities†**

| Institute[a] | Ref no. | Year[b] | Agents[c] | Number | | Os[f] (%) | | DFS[g] (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Che[d] | Obs[e] | Che[d] | Obs[e] | Che[d] | Obs[e] |
| MDACC | 75 | 73 | VACAd | 20 | 23 | 65 | 57 | 55 | 35 |
| Mayo Clinic | 76 | 75 | VACAdD | 24 | 24 | 83 | 83 | 7[h] | 68 |
| NCI | 77 | 77 | VCM | 39 | 28 | 82 | 61 | 74 | 54* |
| EORTC | 63 | 78 | CAVD | 145 | 172 | 63 | 55 | 56 | 43 |
| Bergonie | 62 | 80 | CAVD | 31[i] | 28 | 87 | 54* | 81 | 36* |
| SSG | 78 | 81 | A | 93[i] | 8 | 74 | 70 | 62 | 57 |
| UCLA[j] | 79 | 81 | A | 54 | 63 | 81 | 75 | 56 | 57 |
| Rizolli[j] | 61 | 81 | A | 33 | 44 | 91 | 70* | 73 | 45* |
| DFCI-MGH/ ECOG/ISSG | 80 | 78/83 | A | 48 | 53 | 79 | 67 | 78 | 64 |

† Adapted with permission from Zalupski MM, Ryan JR, Hussein ME, Baker LH: Defining the role of adjuvant chemotherapy for patients with soft tissue sarcoma of the extremities. In Salmon SE (ed.): "Adjuvant Therapy of Cancer VII." Philadelphia: Lippincott, 1993, p 388.
[a]MDACC-M.D. Anderson Cancer Center; NCI-National Cancer Institute; EORTC-European Organization for the Research and Treatment of Cancer; SSG-Scandinavian Sarcoma Group; UCLA-University of California, Los Angeles; DFCI-Dana Farber Cancer Institute; MGH-Massachusetts General Hospital; ECOG-Eastern Cooperative Oncology Group; ISSG-Intergroup Sarcoma Study Group.
[b]Start of study (ECOG/DFCI-MGH 78, ISSG 83). OS-survival, DFS-disease-free survival.
[c]V = vincristine, A = doxorubicin, C = cyclophosphamide, Ad = dactinomycin, D = dacarbazine, M = methotrexate.
[d]Treated.
[e]Untreated control.
[f]Survival.
[g]Disease-free survival.
[h]Metastasis-free survival (see text).
[i]Included nonextremity patients.
[j]Extremity alone.
*Reported by authors as $P < 0.05$.

TNF-alpha, gamma-interferon, and melphalan in combination and administered by isolated limb perfusion in patients deemed unresectable resulted in limb salvage in 21 of 23 patients (93%). Complete pathologic response (100% necrosis) of the tumor was seen in 7 of 14 patients and 90% necrosis seen in 8 of 14. This is a promising technique. However, indications for its use are likely to be limited to patients with unresectable tumors. Local control can be achieved in most situations with radiation and surgery in combination. Currently there are two trials, one in Europe and another in the United States, evaluating this approach.

## WOUND HEALING

An area of concern in the modern management of STS with multiple modalities is the effect of RT and chemotherapy on wound healing and the effect of surgery on planned postoperative adjuvant therapies. This is difficult to analyze when comparing different studies. There are no randomized studies comparing different approaches. Multiple variables play a role in the final outcome. These include patient co-morbid conditions such as obesity and age, tumor characteristics such as size and location, the surgical approach, and the methods used to give adjuvant therapies. It is important to recognize that there is a baseline level of surgical complications following surgical resection of soft tissue sarcomas. A report from the NCI in 1987 noted a 34.4% incidence of complications following resection of extremity STS [56]. Fewer than 10% of patients required re-hospitalization for management of complications. However, patients with postoperative complications had delay of adjuvant radiation by an average of 11 days. In patients with more severe complications, the delay was as long as 210 days. Other complications may occur following completion of radiation therapy. In the MDA series [41], Lindberg et al. reported a 6.5% incidence of significant complications in 200 extremity STS treated with postoperative RT. One amputation was necessary 42 months following completion of radiation. Two fractures were seen late following radiation and were treated successfully. Bujko et al. [57] from MGH reported an overall wound complication rate of 37% in 202 patients with STS treated with preoperative radiation. In 33 patients (16%), secondary surgery was required, including six amputations. Investigators from MSKCC [58] reported a significant complication rate of 14%, but no amputations in a series of patients treated with combined resection and BRT. Early in their experience with this technique, the complication rate was 44% when catheters were loaded before the fifth postoperative day. Loading the catheters after the fifth postoperative day markedly improved the complication rate.

When patients are treated with planned resection to be followed with planned postoperative therapy, radiation,

or chemotherapy, complications that occur will almost certainly delay or may even preclude adjuvant therapy. The percentage of patients having complications following planned postoperative therapy and planned preoperative therapy appear to be similar, although complications following neoadjuvant therapies certainly seem to be more severe. However, careful surgical technique may minimize the occurrence of complications in both groups. Barwick et al. [59] and Bell et al. [60] have demonstrated that the use of vascularized tissue transfer in irradiated wounds can decrease wound complications when appropriately used. These also may be used in patients planned for postoperative therapy or in patients not requiring adjuvant therapy.

## ROLE OF SYSTEMIC ADJUVANT THERAPY

Although significant improvements have been made in local control and limb preservation, distant failure remains the principal reason for poor long-term survival. This is especially true for large, high grade and deep STS. Drugs have been evaluated alone or in combinations in 11 randomized trials of adjuvant chemotherapy. Two of the trials were restricted to extremity sarcomas alone (Table II). The remainder included extremity tumors and other sites. In all but one of these trials, therapy was given following complete resection. RT was given postoperatively in these trials. The duration of treatment varied from 4 months to 2 years. Low grade and small tumors were included in the analysis in early studies.

The drug regimens and doses varied, but they included doxorubicin alone or in multiple combinations with vincristine, cyclophosphamide, dactinomycin, dacarbazine, methotrexate, and leucovorin. Although difficult to analyze, most of these series did not show a survival benefit. The two studies that show some statistical improvement in survival are those of the Rizzoli Institute [61] with 77 patients and the Foundation Bergonie [62] with a total of 59 patients. There is a suggestion of improved local control in some studies. The recently published data from the EORTC [63] is the largest randomized trial of adjuvant chemotherapy and found no difference in local control, metastases free survival, and overall survival in patients with limb sarcomas when multi-drug Adriamycin-based therapy was used. Although controversial, most authors do not believe that the current data support the routine use of adjuvant therapy outside clinical trials.

## MANAGEMENT OF METASTATIC DISEASE

Management of disseminated disease includes the selective use of palliative radiation therapy, chemotherapy, and surgery. Single agent or combination therapy has been used. Doxorubicin is the most effective single agent with a response rate of ~16–24% in several series [64]. DTIC has shown remission rates between 15% and 20% [65]. Ifosfamide has led to single agent responses of 22–47% [66].

Combination therapy has been explored in multiple studies. Two drug regimens have shown variable response rates in phase II and phase III studies. For Doxorubicin-dacarbazine, the best results were reported in 1990 by Weh et al. [67] with a response rate of 35% in a small series. However, the SWOG-CALCG study [68], with 170 patients, reported a 17% response rate. The complete response rate was only 2%. For doxorubicin-ifosfamide, the best response was 43% in 104 patients obtained by the EORTC [69]. In two studies substituting epirubicin for doxorubicin, the response rate was ~48% [70,71].

The combination of the three agents, doxorubicin, dacarbazine, and ifosfamide, with the uroprotective agent, Mesna [72], has shown response rates of 48%. When comparison has been made between single drugs and combinations in different schedules, the multiple drug regimens have shown better response rates, but survival has not improved. In general, the median survival has been 7–12 months. Complete responses have been <10%. Toxicity is higher with these combinations. The variability in some of these results may be related to dose modifications secondary to toxicity.

The role of surgery in patients with systemic disease includes the surgical treatment of isolated lung metastasis. Approximately 20% of patients will develop pulmonary metastasis as the initial and only site of distant metastasis. Large high grade neoplasms are more often associated with the development of pulmonary metastasis. Of 135 patients with pulmonary metastasis treated at MSKCC [73], 58% were treated surgically. The 3-year survival rate after complete resection was 23% with a median survival of 19 months. RT may be useful in the palliative treatment of symptomatic metastasis [74].

## SUMMARY

The incidence of STS has not changed over the last several years, and the etiology remains unclear. The histological subtype may be important in management decisions, although tumor grade, size, and depth are the main prognostic factors. Age, positive margins, and presentation with recurrent disease also may be significant in specific situations. In treatment planning, biopsy and imaging of the tumor are crucial. Surgical resection with RT is the standard of care. The tumor should be resected with clear margins. The optimal RT methodology is still unclear. Preoperative RT appears particularly attractive for the large tumors where amputation may be required for control. The concept of brachytherapy is practical for most high grade tumors, but has no effect on low grade tumors. Postoperative RT can be selectively applied after full histological evaluation of the tumor, although the treatment field is larger. Neoadjuvant combination chemotherapy and radiation given prior to surgery has shown

modest improvement in local control, when compared to surgery and radiation. Adjuvant chemotherapy has not demonstrated improvement in overall survival and should be used only in clinical trials. In a minority of cases, resection of isolated pulmonary metastasis will provide a chance for cure. Isolation limb perfusion with TNF, interferon, and melphalan is a promising technique for local control, but the long-term results are unknown. Further developments in systemic therapy need to be made in order to make significant advances in the cure of this disease.

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